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[54]发明名称 6-硫代黄嘌呤衍生物的制造方法

[57]摘要

一种结构式为  的化合物的制备方法。其中R^3是乙基、正丙基或正丁基，R^9是氢、甲基或乙基。该方法是在吡啶中加入五硫化二磷和黄嘌呤衍生物进行回流加热，再进行后处理。显示出支气管扩张活性，其副作用减小和半衰期延长。通过将上述化合物给病人服用。同样可以提供一种达到支气管扩张而且减小不希望有的作用[多尿，氯乙能苯（CNS）活性]的方法。

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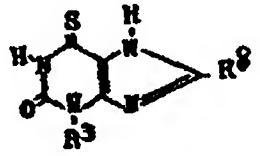
权 利 要 求 书

1.一种生产结构式为  的化合物的方法，其中R^3是乙基、正丙基或正丁基，R^8是氢、甲基或乙基，其特征在于所述的方法是在吡啶中加入五硫化二磷和黄嘌呤衍生物进行回流加热，再进行后处理。

2.根据权利要求1 所述的方法，其特征在于所述的后处理为：然后用水冷却此溶液，将所产生的悬浮液浓缩，然后将固体收集起来，将这种仍然潮湿的产品悬浮在氢氧化钠溶液中，然后将滤液收集起来，且用盐酸酸化，然后将作为结果产生的沉淀物收集起来，并溶解在氢氧化钠溶液中，所产生的溶液用木炭处理，随后过滤，再用盐酸酸化，将作为结果所产生的沉淀物收集起来，用冰水洗涤，并干燥得产物。

3.根据权利要求1 所述的方法，其特征在于所述的后处理为：将此溶液冷却至环境温度；用水处理，将此悬浮体在真空中浓缩，进一步用水稀释，再浓缩，收集粗制产品，并用冰水洗涤，将干燥的材料溶解于三氯甲烷，溶液通过硅胶过滤，蒸发三氯甲烷，剩留物用丙酮一乙醚结晶。

说　　明　　书

6-硫代黄嘌呤衍生物的制造方法

某些黄嘌呤衍生物以前已用作抗气喘的支气管扩张治疗。例如：已知的3-丙基黄嘌呤[埃坡罗嘧啉（Enprofylline）]和1,3－二甲基黄嘌呤（茶碱）均是抗气喘剂和支气管扩张剂，《变态反应（Allergy）》1983年第38期的75—79页，分析了3-丙基黄嘌呤的支气管解痉活性，而《医学假设（Medical Hyprotheses）》1962年第8期515—526页的评论认为3-丙基黄嘌呤的效果为茶碱的4—5倍，而不出现茶碱的腺嘌呤苷拮抗活性。

但是,3-丙基黄嘌呤的一个不利因素是半衰期短，不到2小时，而且也保留了一种极不受欢迎的催吐作用，正和茶碱的情况一样。

唯一的一种特别的1-未取代的硫代黄嘌呤衍生物，特别是3-异丁基-6-硫代黄嘌呤已被制备并测定其支气管扩张活性,[《英国药物学杂志（Brit.J. Phaimacol.）》(1961年),第17期196—207]。这种化合物（表4中第30号化合物与6-硫代可可碱(3,7-二取代的6-硫代黄嘌呤）和6-硫代咖啡碱(1,3,7-三取代的6-硫代黄嘌呤）一起受检测，测定这种化合物的支气管扩张活性的试验只进行了两次，要注意的是所进行的试验次数少。数据没有经过任何统计学分析。

现在人们惊奇地发现，某些6-硫代黄嘌呤衍生物不仅更好地提高了支气管扩张活性，而且也减小了副作用，同时半衰期延长到超过以前所用的相应的黄嘌呤衍生物支气管扩张剂。

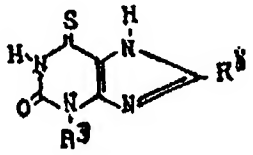
本发明以某些新的黄嘌呤衍生物为目标，能提供更好的支气管扩张活性，而且副作用减小，与已有的支气管扩张剂相比，这些化合物也具有半衰期增长的优点。

因此，本发明的目的在于向各个气喘病患者或有气喘症状的病人提供增进支气管扩张的药物。

本发明的目的还在于增进支气管扩张作用和减小不希望有的副作用。

本发明的另一目的在于提供取得提高支气管扩张活性的新化合物、组合物和方法，这些化合物和组合物的稳定性已提高到超过规定的时间。

本发明已达到这些和其它目的，本发明是以结构式为



的化合物为研究目标，其中R^1是乙基、正丙基或正丁基，R^8是氢、甲基或乙基，这样一种化合物显示出更好的支气管扩张活性，而且副作用减小，同时稳定也提高了，特别是其半衰期延长到超过以前所用的相应的化合物和组合物。本发明也通过给病人服用他所需要的、对支气管扩张有效的上述结构化合物量，以提供一种达到支气管扩张并且副作用减小的方法。

本发明的化合物增加了体内稳定性，也就是，半衰期延长到超过一直用于支气管扩张的其它相应的黄嘌呤衍生物，特别是3-丙基黄嘌呤。另外，本发明提供了与其它黄嘌呤化合物，例如:3- 丙基黄嘌呤比较提高了支气管扩张活性而且不希望的副作用减小的化合物。

本发明的3-乙基- 、3-丙基- 和3-正丁基-6- 硫代黄嘌呤可以任意地在上述结构式中明确表示的8 号位上用甲基或乙基取代。特别好的化合物是3-乙基-6- 硫代黄嘌呤和3-丙基-6- 硫代黄嘌呤。本发明的这些化合物，可以根据伍德里奇(Wo ldridge) 和史莱克

(Slack) 在《化学协会杂志》(J . Chem. Sos .)1962年1863—1868页中所提出的方法，用恰当的前体来合成。

本发明的化合物可以连同任何常用的在药物上可接受的载体或赋形剂掺入到一种药物组合物中来给患者服用，这些化合物可以以游离的或无毒的、在药物学上可接受的盐的形式掺入到这样的药物组合物中，本发明的这些化合物的在药物学上可接受的盐可以通过与等量的有机或无机碱进行通常的反应来制备，这些药物学上可接受的盐包括：钾、钠、胆碱和基本的氨基酸盐，但不限于此。

本发明的组合物可以与一般的可注射的液态载体，例如，水或适合的醇一起供非肠道作用，这些可注射的组成可以包括用作注射的一般辅药，例如：稳定剂、增溶剂和缓冲剂，这些组合物可以进行肌肉注射、腹膜内注射或静脉注射。

根据本发明的组合物也可以配成含有一种或多种在生理学上可配伍的载体或赋形体的口服固态或液体组合物，这些组合物可以含有诸如结合剂、填充剂，润滑剂和可接受的润湿剂的一般配料，这些组合物可以呈任何方便的形式，例如，片剂、胶囊剂、锭剂、水或油悬浮物、乳剂或在使用前适于用水或其它适合的液态溶剂重新配制的干燥粉剂，以直接或控制释放。

用于口服的液态形式也含有诸如甜味剂、香料、防腐剂和乳化剂一类添加剂，此外，也可以配制成用于口服的、含有食用油的非水液态组合物，这些液态组合物可以以一单位剂量方便地封装在如：胶囊中。

本发明的组合物也可以以气溶胶形式局部服用。在本发明的一个特殊方面，通过给病人服用他所需要的、对支气管扩张有效的上述结构化合物量，以达到支气管扩张，并减少了呕吐反应。

为了本发明的目的，通常所用的剂量可在很大的范围内变化，这

取决于各种因素，例如：病人的个人因素，合适的口服剂量可以是50—1000毫克，每天1 —4 次，而合适的非肠道使用剂量可以是20—500 毫克。

本发明将通过下面举实施例的方式进一步详细地加以说明：

实施例1

3-乙基-6- 硫代黄嘌呤

将含有11.7克(65 毫克分子)3- 乙基黄嘌呤的110 毫升吡啶放在含有23.5克(106毫克分子) 五硫化二磷的135 毫升吡啶的悬浮体中处理，温度从25℃升至40℃。

对反应混合物回流加热(伴随溶解作用)4小时，然后把350 毫升水缓慢加入进行冷却，将所产生的亮绿色的悬浮液缩至200 毫升左右，然后将固体收集起来。

将这种仍然潮湿的产品悬浮在100 毫升当量浓度为2 的氢氧化钠溶液中，然后将滤液收集起来，且用当量浓度为5 的盐酸酸化至 pH 值为2 —3 。

然后将作为结果产生的沉淀物收集起来，并溶解在50毫升当量浓度为2 的氢氧化钠溶液中，所产生的溶液用0.4 克木炭处理，随后过滤，再用当量浓度为2 的盐酸酸化到 pH值为2 。

将作为结果所产生的沉淀物收集起来，用冰水洗涤，并干燥，结果得到熔点为278 —280 ℃的- 乙基-6- 硫代黄嘌呤10.3克(收获率为80.7%)。

对$C_7H_8N_4OS$(分子量为196.24) 进行计算的分析：

计算值C42.85% H4.11% N28.55% O8.15% S16.34%

实际值C42.97% H4.14% N28.44% O7.96% S16.49%

实施例2

3-丙基-6- 硫代黄嘌呤

将含有9.32克(48 毫克分子)3- 丙基黄嘌呤的80毫升吡啶放在含有17.33 克(78 毫克分子) 五硫化二磷的80毫升吡啶的悬浮体中处理，以实施例1 相类同的方法处理，可得到8.9 克3-丙基-6- 硫代黄嘌呤，通过甲醇- 丙酮再结晶可产生熔点为249 —250 ℃的针状结晶体7.4 克(收获率为59%)。

对$C_8H_8N_4OS$(分子量为210.26) 进行计算的分析：

计算值：C45.7%　H4.79% N26.65%　O7.61%　S15.25%

实际值：C45.88%　H4.84% N26.66%　O7.36%　S15.26%

实施例3

3-丁基-8- 乙基-6- 硫代黄嘌呤

将11.8克(50 毫克分子)3- 丁基-8- 乙基黄嘌呤(熔点为304 —309 ℃) 和18.2克(82 毫克分子) 五硫化二磷加入到170 毫升吡啶中回流加热2 小时，将此溶液冷却至环境温度，用110 毫升水缓慢地处理(放热的)，将此悬浮体在真空中于60℃时浓缩至100 毫升，进一步用140 毫升水释释，再浓缩至120 毫升左右，收集粗制产品，并用冰水洗涤，将干燥的材料(11.1 克) 溶解于100 毫升左右的三氯甲烷，溶液通过55克硅胶过滤，蒸发三氯甲烷，剩余物用丙酮- 乙醚结晶，即得7.2 克(57.5%)3- 丁基-8- 乙基-6- 硫代黄嘌呤，熔点为206 —207 ℃，从此母液可得到第二批产品2.1 克(16.3%)。

对$C_{11}H_{16}N_4OS$(分子量为252.3)进行计算的分析：

计算值：C52.36%　H6.39% N22.20%　S12.70%

实际值：C52.26%　H6.48% N22.25%　S12.66%

实施例4

3-乙基-8- 甲基-6- 硫代黄嘌呤、3-乙基-8- 乙基-6- 硫代黄嘌呤、3-丙基-8- 甲基-6- 硫代黄嘌呤、3-丙基-8- 乙基-6- 硫代黄嘌呤、3-丁基-6- 硫代黄嘌呤和3-丁基-8- 甲基-6- 硫化黄嘌呤都可以

用与加实施例1 、2 和3 所述的3-乙基-6- 硫代黄嘌呤、3-丙基-6-硫代黄嘌呤或3-丁基-8- 乙基-6- 硫代黄嘌呤同样的合成方法来进行合成。

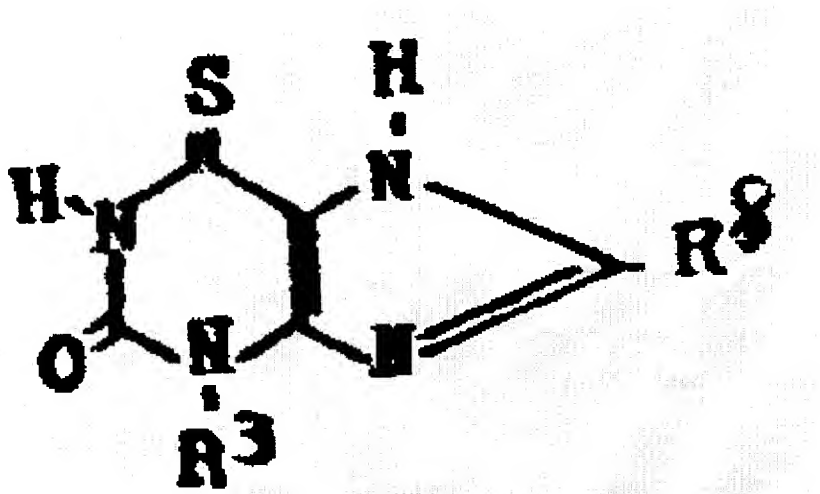
本发明的上述描述仅仅看作为典型的实例，但不论怎么说这并不意味着它仅限于这个范围。

[54] Title of the Invention

The manufacturing method of 6- xanthine derivatives

[57] Abstract

The preparation method of compounds of structural formula



wherein, R3 is ethyl, n-propyl or n-butyl and R8 is hydrogen, methyl or ethyl.

The said method is to add phosphorus pentasulfide and xanthine derivatives to pyridine and heat under reflux, then carry out post-processing.

It displays bronchodilation activity, with side effects reduction and half- life prolongation.

Giving the above-mentioned compound to the patient can simultaneously provide one method of attaining bronchodilation and reduction of undesired actions [polyuria, chloro acetophenone (CNS) activity].

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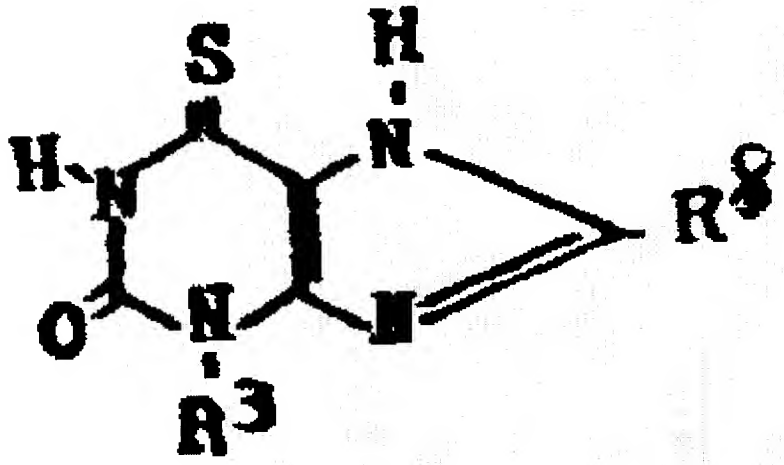
Claims

1. A production process of compounds of structural formula



wherein, R3 is ethyl, n-propyl or n-butyl, R8 is hydrogen, methyl or ethyl, characterised in that the said method is to add phosphorus pentasulfide and xanthine derivative to pyridne and heat under reflux heat, then carry out post processing.

2. A method in accordance with Claim 1, characterised in that the said post-processing is to: cool this solution with water, concentrate the liquid suspension which forms, collect the solid, suspend this still damp product in sodium hydroxide solution, collect the filtered liquid, acidify with hydrochloric acid, collect the precipitate of the resulting product and dissolve in sodium hydroxide solution, treat the solution obtained with charcoal, thereafter filter, then acidify with hydrochloric acid, collect the precipitate of the resulting product, wash with ice water, and dry the product.

3. A method in accordance with Claim 1, characterised in that the said post-processing is to: cool this solution to ambient temperature, treat with water, condense this suspension under vacuum, dilute further using water, condense again, collect the crude product and wash with ice water, dissolve the dried material in trichloromethane, filter the solution through silica gel, evaporate the trichloromethane and crystallise the residue using acetone -ethyl ether.

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Manufacturing method of 6-thioxanthine derivatives

Some xanthine derivatives have already been used as bronchodilation treatment against asthma before. For example: the already known 3-propyl xanthine (Enprofylline) and 1, 3-dimethyl xanthine (theophylline) are both anti- asthma agents and bronchodilation agents, "Allergy" 1983, 38 p75-79 analyzed the bronchorelaxant activity of 3-propyl xanthine, and "Medical Hyprotheses *(sic)*"1962, 8, p515-526 commented that the effect of 3-propyl xanthine is 4-5 times that of theophylline, but the adenosine antagonism of theophylline does not appear.

But, the disadvantage of 3-propyl xanthine is that the half- life is short, no longer than 2 hours, and also another reservation making it unacceptable is its emetic action, similar to the case of theophylline.

Only the distinctive 1-unsubstituted thioxanthine derivative, in particular 3-isobutyl-6-thioxanthine has already been prepared and its bronchdilation activity measured [(Brit.J.Phaimacol. *(sic)*) (1961), 17, p196~207].

This kind of compound (compound No.30 in Table 4 with 6-thiotheobromine (3,7-disubstituted 6-thio xanthine) and 6-thiocaffeine(1, 3, 7-trisubstituted 6-thioxanthine) has been examined, measurement of bronchodilation activity of this kind of compound has been tested only twice, and it is noticed that the number of experiments is little and the data did not have any statistical analysis.

Now, people have surprisingly discovered that some 6-thioxanthine derivatives not only provide improved bronchodilation activity, but also reduced side effects, prolonged half- life which exceeds that of the previous corresponding xanthine derivative bronchodilators.

This invention targets some new xanthine derivatives, which can provide better bronchodilation activity, and reduced side effects, compared with existing bronchodilators and these compounds also possess the advantage of extended half- life.

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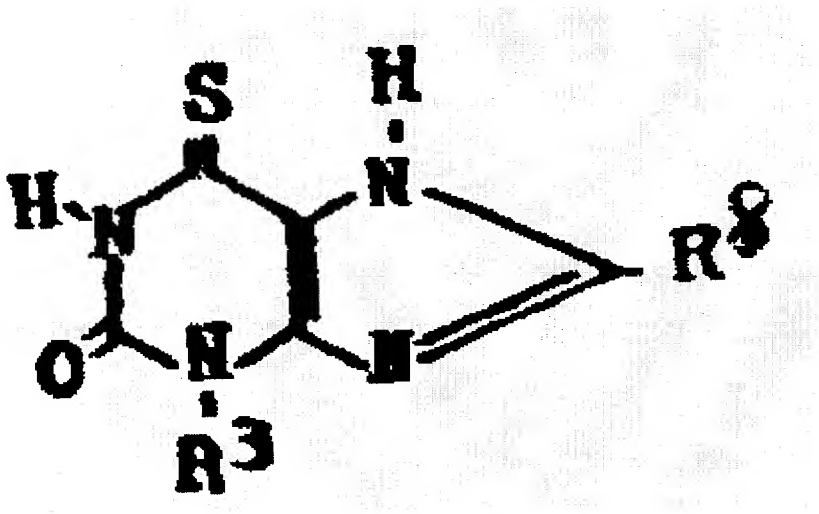
Consequently, the objective of this invention lies in developing the drug to promote bronchodilation for each asthma sufferer or patient with the symptoms of asthma.

The objective of this invention also lies in enhancing the bronchodilation action and reducing unwanted side effects.

Another purpose of this invention lies in providing new compounds, compositions and methods to obtain high bronchodilation activity, wherein the stability of these compound and compositions is increased to exceed a stipulated time.

This invention has achieved these and other purposes. The target of this invention is the study of the compound of structural formula



wherein, R3 is ethyl, n-propyl or n-butyl, R8 is hydrogen, methyl or ethyl. This kind of compound displays better bronchodilation activity, and reduced side effect reduce and at the same time stabilize or raise especially to prolong its half- life to exceed that of corresponding compounds and compositions used previously. This invention also provides a method to attain bronchodilation and side effect reduction, by the patient taking the quantity of the compound of the above-mentioned structure that is needed, for bronchodilation effect.

The compound of this invention has increased stability in vivo, and also has a prolonged half- life over the other corresponding

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xanthine derivatives that have been used for bronchodilation, especially 3-propyl xanthine.

Moreover, this invention provides other xanthine compounds, for example: compounds with raised bronchodilation activity and reduced unwanted side effects relative to 3-propyl xanthine.
The 8 position of the 3-ethyl-, 3-propyl-and 3-n-butyl-6-thio xanthine of this invention with the above-mentioned structural formula can definitely be optionally substituted by methyl or ethyl.
Specially good compound is 3-ethyl-6-thio xanthine and 3-propyl-6-thio xanthine.

These compounds of this invention can be synthesised according to the method put forward by Woldridge and Slack in J.Chem.Sos. (sic) 1962 p1863-1868, using suitable precursors.

The compound of this invention can be administered to a patient in a drug composition together with any commonly used pharmaceutically acceptable carrier or excipient.

These compounds can be added to this kind of medicinal composition in free form or in the form of a non-toxic pharmaceutically acceptable salt. These compounds of this invention can be prepared as the pharmaceutically acceptable salt in the usual way through carrying on the usually used reaction with an equal quantity of organic or inorganic base. These pharmaceutically acceptable salts include: potassium, sodium, choline and basic amino acid salt, but are not limited to these.

The composition of this invention can provide the parenteral route with general injectable liquid carrier, for example, water or together with alcohol.

These injectable constituents can include generally used injection adjuvants, for example: stabiliser, solubiliser and buffer, these compositions can be for intramuscular injection, intraperitoneal injection or intravenous injection.

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The composition of this invention can also be a solid or liquid composition for oral use in a formulation with one or more physiologically acceptable carrier or excipient. These compositions can contain general preparation materials such as binder, filler, lubricant and acceptable wetting agent.

These compositions can be offered in any convenient form, for example, tablets, capsules, shaped tablets, water or oil suspensions, emulsions or are suitable for the dry powder agent for regeneration with water or suitable liquid solvent before using, with direct or controlled release.

The liquid form used for oral administration also contains additives such as sweetener, flavour, preservative and emulsifier, and in addition, the preparation for oral administration can also contain non-aqueous liquid composition of edible oil, a convenient quantity of these liquid compositions can be sealed in a pack such as the capsule.

The composition of this invention can also be administered locally in aerosol form.

A special aspect of this invention is that by administering the quantity of compound with bronchodilation effect of the above-mentioned structure which is required by the patient, effective bronchodilation can be obtained and emetic reaction reduced.

For the objective of this invention, the amount of agent usually used can be varied within a very wide range. This is decided by various factors, for example: the patient's personal factors. Suitable amount of agent to take orally can be 50-1000 mg, 1-4 times per day, and suitable amount of agent to take parenterally can be 20-500 mg.
The way of implementing this invention will be explained in more detail using examples:

Example 1

3-ethyl-6-thio xanthine

110 ml pyridine containing 11.7 g (65 milligram-molecules (sic, *surely mmol*) of 3-ethyl xanthine was processed with a suspension

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of 135 ml pyridine containing 23.5 g (106 milligram-molecules (sic, *surely mmol*) of phosphorus pentasulfide and the temperature was raised from 25°C to to 40°C.

The reaction mixture was heated under reflux (accompanied by dissolution) for 4 hours, then 350 ml water was added gently. The bright green suspension formed was concentrated to about 200 ml, then the solid was collected.

This still damp product was suspended in 100 ml of 2N sodium hydroxide solution, then filtered to collect the liquid, and acidified to pH 2-3 with 5N hydrochloric acid.

Then the precipitate of the resulting product was collected, and dissolved in 50 ml of 2N sodium hydroxide solution. The resulting solution was treated with 0.4 g of charcoal, and subsequently acidified to pH 2 with 2N hydrochloric acid.

The resulting precipitate was collected, washed using ice water, and dried, to obtain 10.3 g of -ethyl-6-thioxanthine *(sic)* with melting point 278-280°C (yield is 80.7%)

Analysis calculation performed with respect to C7H8N4OS (molecular weight 196.24):

Calculated value: C42.85% H4.11% N28.55% O8.15% S16.34%.
Actual value: C42.97% H4.14% N28.44% O7.96% S16.49%

Example 2
3-propyl-6-thioxanthine

80 ml pyridine containing 9.32 g(48 milligram-molecules (sic, *surely mmol*) of 3-propyl xanthine was treated with a suspension of 80 ml pyridine containing 17.33 g (78 milligram-molecules (sic, *surely mmol*) of phosphorus pentasulfide, and processed in the same way as in Example 1, to obtain 8.9 g of 3-propyl-6-thioxanthine. This was recrystallised from methanol-acetone to produce 7.4 g of needle-shaped crystals with melting point 249-250°C (yield 59%).

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Analysis calculation performed with respect to C8H10N4OS (molecular weight 210.26):

Calculated value: C45.7% H4.79% N26.65% O7.61% S15.25%.
Actual value: C45.88% H4.84% N26.66% O7.36% S15.26%.

Example 3

3-butyl-8-ethyl-6-thioxanthine

11.8 g (50 milligram-molecules (sic, *surely mmol*) 3-butyl-8-ethyl xanthine (melting point 304-309°*C*) and 18.2 g (82 milligram-molecules (sic, *surely mmol*) of phosphorus pentasulfide were added to 170 ml pyridine and heated under reflux for 2 hours. This solution was cooled to ambient temperature, treated gently using 110 ml water (release heat) and this suspension was concentrated under vacuum at 60°*C* to 100 ml, discharged into a further 140 ml water, and again concentrated to about 120 ml. The crude product was collected, washed with ice water, and the dried material (11.1 g) was dissolved in about 100 ml of trichloromethane. The solution was filtered through 55 g of silica gel and the trichloromethane was evaporated. The residue was crystallised using the acetone-ethyl ether, to obtain 7.2 g(57.5%)3-butyl-8-ethyl-6-thioxanthine, melting point 206-207°*C*. 2.1 g of a second product was obtained from the mother liquor (16.3%).

Analysis calculation performed with respect to C11 H16 N4 O S (molecular weight 252.3):
Calculated value: C52.36% H6.39% N22.20% S12.70%.
Actual value: C52.26% H6.48% N22.25% S12.66%.

Example 4

Synthesis of 3-ethyl-8-methyl-6-thioxanthine, 3-ethyl-8-ethyl-6-thioxanthine, 3-propyl-8-methyl-6-thioxanthine, 3-propyl-8-ethyl-6-thioxanthine, 3-butyl-6-thioxanthine and 3-butyl-8-methyl-6-thioxanthine was performed in the same way as 3-ethyl-6-thioxanthine, 3-propyl-6-thioxanthine or 3-butyl-8-ethyl-6-thioxanthine in Example 1, 2 and 3.

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The above-mentioned description of this invention is only to be regarded as typical actual examples, and is not meant to be limited to this range.

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